Type 2 diabetes treatment
French Recommendations for good practice
AFSSAPS - HAS. 2006

Definition
Diabetes is defined by a fasting blood glucose level over 1.26 g/l (7 mmol/l) after 8 h of fasting and verified twice. It is also defined by the presence of diabetes symptoms (polyuria, polydipsia, weight loss) associated with blood glucose (venous plasma) greater than or equal to 2 g/l (11.1 mmol/l) as well as by blood glucose greater than or equal to 2 g/l (11.1 mmol/l) 2 h after a 75-g oral glucose load (criteria proposed by the World Health Organization).

Epidemiology
Type 2 diabetes is a veritable epidemic related both to changes in lifestyle and longer life expectancy. In Europe, it is estimated that there are more than 21 million type 2 diabetics. The cardiovascular complications are the main cause of death in type 2 diabetes patients. In France, the percentage of diabetics among patients on dialysis has risen from 6.9% in 1989 to 13.1% in 1997 and 23.6% in 2003. Of diabetics on hemodialysis, 90% are type 2 diabetics.

How to treat
Management of type 2 diabetes should:
– be undertaken early;
– be global in outlook;
– aim to normalize the blood glucose levels and to correct all the cardiovascular risk factors that can be improved;
– be adapted to each patient by modulating treatment according to physiological age, comorbidities, and the severity and duration of the diabetes;
– work with the active participation of the patient*;
– call on the complementarity of the different health professions.

Nonpharmacological management of diabetes

Diet and lifestyle
The active fight against a sedentary lifestyle as well as meal planning are irreplaceable interventions at all stages of type 2 diabetes management.

Education
Education is a fundamental aspect of managing all diabetic patients. It should be implemented as soon as diabetes is discovered by physicians or paramedical professionals trained in this activity.

Medications designed to normalize blood glucose in type 2 diabetes

Metformin
Metformin can normalize or reduce blood glucose levels in type 2 diabetes independently of weight, age, and duration of diabetes (reduction of HbA1c on the order of 1%-1.5%).
This is the only antidiabetic oral drug in single-drug therapy to have demonstrated its effectiveness in reducing cardiovascular mortality in type 2 diabetes.
It does not induce hypoglycaemia of by itself. The most frequent side effects are digestive.

Insulin secretagogues
Glucose-lowering sulfonylureas
Glucose-lowering sulfamides can normalize or reduce blood glucose of type 2 diabetics whether or not the patient is overweight (reduction of HbA1c on the order of 1%-1.5%).

Meglitinides
Repaglinide (Novonorm*) is a faster-acting and shorter-duration insulin secretagogue. The glucose-lowering power of repaglinide is close to that of glucose-lowering sulfonylureas.

* lifestyle measures, smoking cessation, physical exercise, nutrition, weight management, medication compliance.
Prevention and treatment of diabetic microangiopathy and macroangiopathy is based on:
• Health and diet measures, physical exercise, weight loss.
• An attempt to normalize blood glucose defined as a glycated haemoglobin (HbA1c) less than 6.5% (for a healthy subject norm up to 5.5% or 6%).

Early and strict management of risk cofactors:
– Blood pressure: strict blood pressure control < 130/80 mmHg
– Lipids: graduated targets for LDL cholesterol following an increasing cardiovascular risk level:
  - LDL-cholesterol < 1.9 g/l is reserved only for the few patients with no other additional risk factor and no microangiopathy* whose diabetes has been progressing for less than 5 years
  - LDL-cholesterol < 1.6 g/l in the other patients presenting at most one additional risk factor
  - LDL-cholesterol < 1.3 g/l in patients presenting at least two additional risk factors and diabetes progressing for less than 10 years.
  - LDL-cholesterol < 1 g/l
    - in patients in secondary prevention
    - in patients in secondary prevention
    - either with kidney involvement (albuminuria > 300 mg/day or creatinine clearance < 60 ml/min),
    - or diabetes progressing for more than 10 years and at least two additional risk factors
– Smoking cessation

Risk factors =
• Family history of early coronary disease
  • myocardial infarction or sudden death before the age of 55 in the father or a male 1st degree relative,
  • myocardial infarction or sudden death before the age of 65 in the mother or a female 1st degree relative
• Family history of completed stroke before the age of 45
• Smoker or smoking cessation less than 3 years ago
• Permanent high blood pressure, treated or untreated
• HDL-cholesterol < 0.40 g/l (1.0 mmol/l) for either sex
• Microalbuminuria (> 30 mg/24 h)
• Age
  • male aged 50 years or more
  • female aged 60 years or more

Protective factor HDL-cholesterol ≥ 0.60 g/l (1.5 mmol/l): subtract “one risk” from the risk level score

Ideal objectives in type 2 diabetes treatment.

Treatment objectives should be individualized for each patient. The “ideal” objectives, in particular those concerning blood glucose control, listed above should be adapted according to the following criteria:
- physiological age of each subject
- duration of diabetes,
- comorbidities,
- treatment compliance and the degree of the patient’s participation in managing the disease.
- reserved for patients whose life expectancy warrants preventing the complications of micro- and macroangiopathy.
Prevention of hypoglycaemia with insulin secretagogues

The prevention of iatrogenic episodes of hypoglycaemia is an important therapeutic objective for type 2 diabetic patients treated with glucose-lowering sulfonylureas or meglitinides.

Glitazones (thiazolidinediones)

Glitazones act by reducing muscular and hepatic insulin resistance. They have demonstrated their glucose-lowering effects in single-drug therapy (lowering HbA1c on the order of 1%), as well as in double therapy, associated with metformin or glucose-lowering sulfonylureas, and finally in triple therapy (metformin + insulin secretagogue + glitazone).

Glitazones cannot induce hypoglycaemia alone.

Congestive heart failure and antecedents of congestive heart failure (class I-IV) are a formal contraindication to prescribing glitazones.

Macular edema onset or progression has been observed with rosiglitazone and pioglitazone.

Experimental models in the rat have shown onset of bladder tumors with pioglitazone and tumors of the colon with rosiglitazone as well as hypertrophic cardiomyopathy with pioglitazone and rosiglitazone.

Alphaglucosidase inhibitors

The alphaglucosidase inhibitors slow intestinal absorption of complex carbohydrates. Their glucose-lowering power is on the order of −0.5% to −1% HbA1c. They act mainly on postprandial blood glucose. Their side effects are digestive and are frequent, though not serious.

Insulin therapy for type 2 diabetes

Insulin can reduce blood glucose, even normalize the blood glucose in the type 2 diabetic with or without overweight. Insulin therapy has been demonstrated to reduce the onset of ocular microangiopathic and renal complications in type 2 diabetics (UKPDS).

Hypoglycaemia is the most frequent side effect associated with insulin therapy.

Weight gain with insulin treatment is highly variable and is generally close to that observed with glucose-lowering sulfonylureas and glitazones.

Therapeutic strategy to normalize blood glucose

The general objective in patients whose life expectancy warrants prevention of complications of micro- and macroangiopathy obtained by maintaining appropriate blood glucose levels is reaching an HbA1c rate under 6.5%.

The therapeutic strategy described below is therefore designed most particularly for the patient whose diabetes was discovered early, whose initial blood glucose and HbA1c are not exceedingly high.

Moreover, it is not designed for patients with a limited life expectancy and whose diabetes was discovered late or who have high levels of hyperglycaemia at diagnosis. Particular strategies are described for these patients.

Initial treatment: when diabetes is discovered early

Rapid normalization and sustained maintenance of blood glucose is recommended, aiming for HbA1c <6.5%.

Diet and physical activity are the cornerstone of initial treatment of diabetes.

HbA1c between 6% and 6.5% after 6 months of diet and lifestyle measures:

When HbA1c remains >6% despite 6 months of diet and lifestyle management effort with satisfactory patient compliance, the working group recommends prescribing metformin, before reaching the threshold value of 6.5%.

HbA1c >6.5% despite 6 months of diet and lifestyle management: a choice of single-drug treatments

If after 6 months of diet and lifestyle management (after 3 months if blood glucose is higher), HbA1c remains over 6.5%, there is a choice between the different classes of glucose-lowering medications.

Whatever the BMI, drug therapy can begin with:

– metformin
– alphaglucosidase inhibitors (particularly if there is postprandial hyperglycaemia) in cases of intolerance or contraindication
– if the BMI is below 27 kg/m², one may opt for an insulin secretagogue (sulfonylurea or meglitinide) as first-line treatment, mainly if blood glucose is more pronounced and the risk of hypoglycaemia is lower.

Single-drug therapy failure: HbA1c >6.5% after 6 months of single-drug treatments

If, despite a maximal dose of a single-drug treatment, the HbA1c is higher than 6.5% one of the following double therapies can be attempted:

• metformin + insulin secretagogue
• metformin + glitazone
• metformin + alphaglucosidase inhibitor
• insulin secretagogue + glitazone, in cases of established and persistent intolerance to metformin or contraindication to this drug.
• or insulin secretagogue + alphaglucosidase inhibitor (in cases of severe postprandial hyperglycaemia, but this is less effective on HbA1c than other combinations)

A deciding factor in the choice of the combination is the risk/benefit ratio of each drug class. This ratio has not been as thoroughly evaluated for new treatments such as glitazones as for older drug classes, which benefit from years of clinical experience and longstanding drug monitoring.
Double-therapy failure: HbA1c > 7% after 6 months or more of double therapy

Recommendations call for:
- either a trial with oral triple therapy: metformin + insulin secretagogue + glitazone even though this combination has yet to be evaluated over the long term. The objective is to reach HbA1c less than 7%.
- or immediately opt for (not during double therapy including a glitazone) combining insulin, single injection of an intermediary insulin (NPH) or a slow-acting analogue in the evening. Self-monitoring of blood glucose should be introduced for patients who have not yet begun to do so.

Failure of triple therapy: HbA1c ≥ 8%

If after more than 6 months of properly administered maximal oral triple therapy HbA1c remains greater than or equal to 8%, glitazones should be interrupted and insulin started.

Insulin therapy for type 2 diabetes

The first-intention recommendation is to add insulin to oral double therapy at bedtime, either intermediate insulin (NPH) or a slow-acting analogue, while respecting the contraindication of combining glitazones and insulin.

At the stage of insulin therapy in type 2 diabetes, use of the expertise of a diabetes specialist leading to coordination with the family physician should be considered, in particular if problems are encountered. At the stage of fractionated insulin therapy (> 1 injection), the expertise of a diabetes specialist is indispensable.

Particular situations

Elderly subject (age > 75 years and depending on physiological age)

The blood glucose objective should be adopted to age, duration of diabetes, existing complications, associated diseases, life expectancy, and iatrogenic risk (notably of hypoglycaemia). Therefore, the HbA1c objective should be raised if diabetes is discovered late and/or if life expectancy is reduced.

Diabetes discovered at a later stage

Whatever the patient’s age, many cases of diabetes continue to be discovered at a later stage than what has been detailed above: severe blood glucose imbalance and sometimes complications are already present.

The therapeutic strategy in this case is therefore different: if there are no severe diet errors, the patient can be immediately started on metformin + glucose-lowering sulfonylurea double therapy (glucose-lowering effect achieved more rapidly), even insulin therapy, notably in cases of contraindication to one or several classes of oral antidiabetic drugs.

<table>
<thead>
<tr>
<th>Prescription threshold</th>
<th>Therapeutic strategy</th>
<th>Objective</th>
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</thead>
<tbody>
<tr>
<td>HbA1c &gt; 6%</td>
<td>Step 1</td>
<td>HbA1c &lt; 6%</td>
</tr>
<tr>
<td></td>
<td>Diet and lifestyle measures (DLM)</td>
<td></td>
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<tr>
<td>If despite step 1</td>
<td>Step 2</td>
<td>maintain</td>
</tr>
<tr>
<td>HbA1c &gt; 6%</td>
<td>Single drug + DLM; Metformin even AGI</td>
<td>HbA1c &lt; 6.5%</td>
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<tr>
<td>(in early stages of diabetes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If despite step 1,</td>
<td>Choice of SINGLE-DRUG therapy + DLM</td>
<td>lower</td>
</tr>
<tr>
<td>HbA1c &gt; 6.5%</td>
<td>Metformin or AGI or SU or meglitinides</td>
<td>HbA1c &lt; 6.5%</td>
</tr>
<tr>
<td>If despite step 2,</td>
<td>Step 3</td>
<td>lower</td>
</tr>
<tr>
<td>HbA1c &gt; 6.5%</td>
<td>Double therapy + MHD</td>
<td>HbA1c &lt; 6.5%</td>
</tr>
<tr>
<td>If despite step 3</td>
<td>Step 4</td>
<td>lower</td>
</tr>
<tr>
<td>HbA1c &gt; 7%</td>
<td>TRIPLE THERAPY + DLM</td>
<td>or INSULINE ± OAD + DLM</td>
</tr>
<tr>
<td>If despite step 4,</td>
<td>Step 5</td>
<td>lower</td>
</tr>
<tr>
<td>HbA1c &gt; 8%</td>
<td>INSULIN ± OAD + DLM</td>
<td>FRACTIONATED INSULIN + DLM</td>
</tr>
</tbody>
</table>

OAD = oral antidiabetic drugs; AGI = alpha-glucosidase inhibitors; SU = glucose-lowering sulfonylureas; insulin + AOD = start up insulin: intermediate or slow-acting in evening; fractionated insulin: > 1 injection/day or 2-4/day; DLM: diet and lifestyle measures.
The place of glucose self-monitoring

The working group recommends glucose self-monitoring:
- in all patients on insulin therapy
- in patients treated with insulin secretagogues, to look for or confirm hypoglycaemia and adapt dosage of these drugs if necessary.
- in patients for whom insulin is planned in the short or long term.

Drug treatment of the associated vascular risk factors

Diabetic dyslipidemia

Generalities

Prevention of cardiovascular accidents in the type 2 diabetic patient, as in the general population, involves diet and lifestyle measures: smoking cessation, physical exercise, optimizing the diet with a reduction in consumption of saturated fats.

The overall cardiovascular risk will be evaluated by the addition of risk factors; the Framingham equations adapted to the French population can be used.

Secondary cardiovascular prevention and primary prevention in patients at high cardiovascular risk

In view of the lipid-lowering interventional studies devoted specifically to diabetics (the HPS and CARDS studies) and the compilation of trials including diabetic subgroups, whatever the LDL cholesterol level, it is recommended that patients be given a statin that has demonstrated efficacy in reducing the risk of ischemic complication (atorvastatin, simvastatin).

Administration of low doses of aspirin (75-300 mg) is recommended in diabetics at a high cardiovascular risk in primary prevention combined with a lipid-lowering treatment.

Primary prevention in patients with low or moderate cardiovascular risk

- LDL cholesterol objective < 1.9 g/l is reserved for the small number of patients with no other additional risk factor, no microangiopathy* and whose diabetes has been progressing for less than 5 years;
- The objective is to reach LDL cholesterol < 1.6 g/l in other patients presenting at most 1 risk factor in addition to diabetes;
- The objective is to reach LDL cholesterol < 1.3 g/l in patients presenting at least 2 risk factors in addition to diabetes progressing for less than 10 years.

Use of a statin with drug-marketing approval in this indication (atorvastatin, simvastatin) is recommended.

Blood pressure

High blood pressure is a correctable risk factor for onset of coronary disease and microangiopathy. It is a correctable

* a patient with no signs of retinopathy or microalbuminuria has no microangiopathy.
factor for kidney disease, retinopathy, and diabetic cardiopathy.

In the diabetic patient, blood pressure levels should be lowered to below 130/80 mmHg.

Diet and lifestyle measures (notably weight loss and reduction of sodium consumption) should be encouraged in all with type 2 diabetes hypertensive patients.

The five therapeutic classes (ACE inhibitors or AT(1)-blocking (sartan), thiazidic diuretic, cardioselective beta-blocker, calcium channel blocker) can be used in first intention single-drug therapy in hypertension in type 2 diabetes patients.

In the diabetic, combined therapy is often required to reach the blood pressure objective. Including a thiazide diuretic is recommended in these combinations.

Smoking and the diabetic patient
Smoking is a correctable risk factor for onset and deterioration of diabetic macroangiopathy and renal microangiopathy of type 2 diabetes.

Assistance in smoking cessation should be proposed to type 2 diabetes patients who smoke.

**Drug treatment of type 2 diabetes complications**

Management of the diabetic with multiple complications requires a multidisciplinary approach involving all the specialists concerned.

**Diabetic nephropathy**

Monitoring the kidneys of the type 2 diabetic patient is based on testing microalbuminuria and creatinine level.

Renal function is evaluated by the Cockcroft and Gault formula, taking into account its limitations (age > 80 years, obesity, reduced or excessive muscle mass).

Coordinated management between the family physician, the diabetes specialist, and the nephrologist is recommended in patients with severe or progressive kidney disease.

Prevention and treatment of renal microangiopathy is based on:
- strict blood glucose balance;
- strict blood pressure control;
- lowering albuminuria, whatever its level, is a therapeutic objective.

**Diabetic retinopathy**

Annual fundus examination is recommended in all type 2 diabetes patients for early diagnosis of retinopathy.

Coordinated management between the family physician, the diabetes specialist, and the ophthalmologist is recommended in case of diabetic retinopathy. Frequent fundus examination is advisable if there is progressive retinopathy.

Prevention of retinopathy in the type 2 diabetic patient is based on strict blood glucose balance and blood pressure control.

**The diabetic cardiovascular patient**

Coordinated management between the family physician, the cardiologist, the diabetes specialist, the cardiac surgeon, the vascular surgeon, and the interventional radiologist is recommended for type 2 diabetes patients who have coronary disease, congestive heart failure, and peripheral artery disease.

**Coronary disease**

Use of cardioselective beta-blockers in the type 2 diabetic with coronary disease after myocardial infarction is recommended because this class of drugs reduces cardiovascular mortality.

In the type 2 diabetic patient with coronary disease, secondary prevention with a statin is recommended because its efficacy in this indication has been demonstrated (atorvastatin, simvastatin).

Aspirin (75-300 mg/day) is recommended in the type 2 diabetic with coronary disease as a secondary cardiovascular preventive measure.

Intensive administration of insulin is recommended during the acute phase of myocardial infarction.

**Peripheral vascular disease (lower limbs, carotids)**

Use of aspirin at a low dose (75-160 mg) or clopidogrel is recommended in the type 2 diabetic with arterial disease as primary and secondary prevention.

**Erectile dysfunction**

The type 5 phosphodiesterase inhibitors (IPDE5) (sildenafil, tadalafil, vardenafil) have demonstrated their efficacy for erectile dysfunction in the diabetic patient. They can be used in first-intention treatment except in patients with progressive coronary disease or those treated with nitro compounds.